

## REMARKS

Claims 1 to 16, 18 to 45, 47 to 58, 67 to 76, 80 to 84, 86, 92 to 94 and 96 have been cancelled without prejudice or disclaimer. Claims 17, 46, 59 to 66, 77 to 79, 85, 87 to 91, 95, and 97 are pending and under consideration.

Claim 17 has been amended to remove certain language from the claim. That amendment adds no new matter. Claims 46, 63, and 90 have been amended to change the language "comprising" to the language "consisting of." Those amendments add no new matter. Support for the amendment to claim 85 is found, e.g., at page 19, lines 24 to 25. Support for the amendments to claims 87 and 90 is found, e.g., at page 60, lines 5 to 12.

Applicants provide a replacement page for page 41. Applicants also provide a replacement page for page 43. Those pages are amended to include SEQ ID NOs for the sequences that appear on those pages. Because those replacement pages add new SEQ ID NOs, applicants also provide a substitute Sequence Listing and computer readable form (CRF) of the Sequence Listing. Applicants have amended the specification to include the substitute Sequence Listing into the specification. The undersigned states that the information recorded in the CRF of the Sequence Listing is identical to the substitute paper copy of the Sequence Listing, and that the Sequence Listing adds no new matter.

Applicants have amended the paragraph that appears at page 42, lines 2 to 6. That amendment is made to remove the reference to "grey boxes" in the sequence alignment on page 43. Applicants also amended the term "amino sequence" to the term "amino acid sequence." Those amendments add no new matter.

## **Specification**

The Examiner objects to page 43 because the specification refers to presence of gray boxes and black boxes in the sequence alignment on page 43, but alleges that all of the boxes in the sequence alignment are black. See Advisory Action at page 2, item 2. Applicants have amended the specification to include the language “regions of identity and regions of similarity are shown in black boxes.” That amendment should obviate the Examiner’s objection.

The Examiner objects to the specification for not complying with the sequence rules. See Advisory Action at page 2, item 3. Specifically, the Examiner objects to pages 41 and 43, which disclose sequences without SEQ ID NOs. See *id.* Applicants provide substitute copies of pages 41 and 43 with SEQ ID NOs inserted.

## **35 U.S.C. § 112, second paragraph rejection of claim 17**

The Examiner maintains the rejection of claim 17 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. See Advisory Action, pages 2 to 3, items 5 and 6. Solely to expedite prosecution, and without acquiescing to the Examiner’s rejections, applicants have amended claim 17 to remove the language “at least one of” from the claim. Applicants respectfully assert that that amendment obviates the Examiner’s rejection.

Applicants request reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of claim 17.

**35 U.S.C. § 112, second paragraph rejection of claim 46**

The Examiner also maintains the rejection of claim 46 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. See Advisory Action, pages 2 to 3, items 5 and 7. Applicants respectfully traverse.

In the May 2003 Action, the Examiner rejected claim 46 as allegedly being indefinite. See May 2003 Action at page 4, item 9. Specifically, the Examiner alleged, "Claim 46 is indefinite in the recitation of 'at least one of SEQ ID NO: 19 and 71' since as written, the term 'at least one of' implies that the antibody can bind to a protein comprising both SEQ ID NO: 19 and SEQ ID NO: 71." See *id.* In the November 2003 Amendment, applicants responded that the Examiner's reading of the claim is correct. See November 2003 Amendment at page 9. As stated in the November 2003 Amendment, "[t]he language of the claim is designed to include such an antibody that can bind a protein comprising both of the SEQ ID NOS. It also includes antibodies that bind a protein comprising SEQ ID NO: 19. It also includes antibodies that bind a protein comprising SEQ ID NO:71." See *id.* Despite the fact that applicants confirmed that the Examiner understood the claim correctly, the Examiner continues to allege that correction of claim 46 is required. See Advisory Action at page 3. Because the Examiner apparently agrees that the claim language encompasses embodiments wherein an antibody binds to a protein having an amino acid sequence comprising both SEQ ID NO: 19 and 71, applicants assert that the claim is not indefinite.

Applicants request reconsideration and withdrawal of the 35 U.S.C. § 112, second paragraph, rejection of claim 46.

**35 U.S.C. § 112, first paragraph rejection of claims 80, 85, 87 to 92 and 97**

**(written description)**

**Claim 80**

The Examiner maintains the rejection of claim 80 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support in the specification. See Advisory Action at pages 3 to 4, item 8. Applicants canceled claim 80 without prejudice or disclaimer in the November 2003 Amendment. Thus, the Examiner's rejection of claim 80 is moot.

**Claim 85**

The Examiner maintains the rejection of claim 85 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support in the specification. See Advisory Action at pages 3 to 5, items 8 and 9.

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See MPEP § 2163.I. As applicants noted in the November 2003 amendment, "[f]or some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession." See MPEP § 2163.II.A(3)(a).

In the Advisory Action, the Examiner argues that "14 amino acids (SEQ ID NO: 73) are not sufficient to adequately describe the genus of proteins having the function

recited in view of the fact that there is no teaching indicating that this structural element is related to the function recited." See Advisory Action, page 4. That is incorrect. Applicants identified the 14 amino acid sequence identified by SEQ ID NO: 73 as having sequence similarity to a putative uridine-binding motif. See page 44, lines 1 to 9. As the specification notes, "[the putative uridine-binding] motif is conserved in the translated amino acid sequence of *P. furiosus* P45, which reveals the presence of a putative uridine-binding sequence conserved in  $\psi$  synthetases, dCTP deaminases, and dUTPases." See *id*. The putative uridine-binding motif is related to dUTPase activity because it is conserved in  $\psi$  synthetases, dCTP deaminases, and dUTPases. See *id*. And dUTPase activity is related to PEF function. See specification, e.g., page 19, lines 14 to 20. Thus, the structural element identified as SEQ ID NO: 73 is related to the PEF function.

In any event, solely to expedite prosecution, and without acquiescing to the Examiner's rejection, applicants have amended claim 85 to include the language "wherein the protein is at least 39% similar to SEQ ID NO: 71." As applicants note in the specification, "a sequence similarity of approximately 39% suffices to positively identify a dUTPase activity that can act as a PEF." See page 19, lines 24 to 25. Applicants assert that the combination of identifying characteristics recited in amended claim 85 is sufficient to demonstrate that Applicants had possession of the claimed proteins.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C § 112, first paragraph rejection of claim 85.

Claims 87 to 92 and 97

The Examiner maintains the rejection of claims 87 to 92 and 97 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support in the specification. See Advisory Action at pages 3 to 4. Addressing claims 87 to 92 and 97, the Examiner states, "while the Examiner agrees that the specification discloses the determination of dUTPase activity in a *T. thermophilis* cell extract and the detection in a Western blot of a protein in that cell extract using an antibody against the *P. furi*ous protein P45 of SEQ ID NO: 71, the specification fails to disclose the isolation of a *T. thermophilis* dUTPase or its amino acid structure." See May 2003 Action, at page 6. Applicants respectfully traverse.

As applicants noted above, "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See MPEP § 2163.I.

Applicants have canceled claim 92 without prejudice or disclaimer. Thus, the Examiner's rejection of that claim is moot.

Claim 87 recites "[a] PCR enhancing, protein extract comprising purified proteins from *Thermus thermophilis* wherein at least one protein of the purified proteins from *Thermus thermophilis* possesses dUTPase activity." Claims 88 to 91 and 97 ultimately depend from claim 87. Whether or not the specification discloses isolation of a *Thermus thermophilis* dUTPase or its amino acid structure is irrelevant to the issue of whether claims 87 to 91 and 97 have written description support in the specification. Specifically, claim 87 does not include language directed to an isolated *Thermus*

*thermophilis* dUTPase or its amino acid structure. Rather, it is directed to an extract. The specification describes exactly such an extract. Specifically, the specification describes *Thermus thermophilis* samples which comprise dUTPase activity. See page 60, lines 9 to 12. Thus, applicants have demonstrated possession of “[a] PCR enhancing, protein extract comprising purified proteins from *Thermus thermophilis* wherein at least one protein of the purified proteins from *Thermus thermophilis* possesses dUTPase activity.”

Applicants request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of claims 87 to 91 and 97.

**35 U.S.C. § 112, first paragraph rejection of claims 85, 87-92, and 97**

**(enablement)**

The Examiner maintains the rejection of claims 85, 87 to 92, and 97 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. See Advisory Action at page 5, item 10. Applicants respectfully traverse.

First, as applicants asserted in the November 2003 Amendment, as long as the specification discloses at least one method of making the invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. MPEP § 2164.01(b). “Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. § 112.” See *id.*

Because the Examiner makes seven different rejections for lack of enablement, applicants have addressed the seven rejections individually. Furthermore, because the

Examiner does not specify which rejections correspond to which claims, applicants have made certain assumptions as to which claims the rejections correspond to.

Rejection (1)

The Examiner rejects certain unspecified claims by alleging that the specification does not reasonably provide enablement for a polypeptide having polymerase enhancing factor activity comprising the amino acid sequence of SEQ ID NO: 73 (14 amino acids). See Advisory Action at page 5, item 10. Because that language is similar to the language in claim 85, applicants assume that the Examiner is applying that rejection to claim 85.

As applicants previously argued in the Amendment filed on March 10, 2003 ("the March 2003 Amendment"), it would not require one of skill in the art an undue amount of experimentation to determine whether a protein comprising the amino acid sequence of SEQ ID NO: 73 possessed polymerase enhancing activity. As applicants pointed out in that amendment, screening assays for polymerase enhancing activity are described in the specification in Example 1, pages 20 to 22. Furthermore, the Examiner acknowledges that testing a limited number of polypeptides for polymerase-enhancing activity does not constitute undue experimentation. See May 2003 Action at page 10.

However, the Examiner continues to allege that the claim is not enabled because "testing the extremely large number of polypeptides which comprise the peptide of SEQ ID NO: 73 would constitute undue experimentation absent any teaching as to whether the peptide of SEQ ID NO: 73 correlates with the desired activity." See Advisory Action, page 6, item 12.

First, applicants assert that SEQ ID NO:73 does correlate with the desired activity. As applicants explained above, applicants identified the 14 amino acid sequence identified by SEQ ID NO: 73 as having sequence similarity to a putative uridine-binding motif. See page 44, lines 1 to 9. As the specification notes, “[the putative uridine-binding] motif is conserved in the translated amino acid sequence of *P. furiosus* P45, which reveals the presence of a putative uridine-binding sequence conserved in  $\psi$  synthetases, dCTP deaminases, and dUTPases.” See *id*. The putative uridine-binding motif is related to dUTPase activity because it is conserved in  $\psi$  synthetases, dCTP deaminases, and dUTPases. See *id*. And dUTPase activity is related to PEF function. See specification, e.g., page 19, lines 14 to 20. Thus, the structural element identified as SEQ ID NO: 73 is related to the PEF function.

Second, the Examiner fails to establish that it would constitute undue experimentation to test proteins comprising SEQ ID NO: 73 for PEF function. As noted above, the Examiner acknowledges that testing a limited number of polypeptides for polymerase-enhancing activity does not constitute undue experimentation. The Examiner, however, fails to explain why testing more than a limited number of polypeptides would rise to the level of undue experimentation. Thus, applicants respectfully assert that the claim is enabled.

In any event, without acquiescing to the Examiner’s rejection, applicants have amended claim 85 to include the language “wherein the protein is at least 39% similar to SEQ ID NO: 71.” As applicants noted above, the specification correlates a sequence similarity of approximately 39% to polymerase-enhancing factor activity. See e.g., page

19, lines 24 to 25. That amendment should obviate the Examiner's rejection of claim 85.

Applicants request reconsideration and withdrawal of the first 35 U.S.C. § 112, first paragraph, enablement rejection in item No. 10.

Rejection (2)

The Examiner rejects certain unspecified claims by alleging that the specification does not reasonably provide enablement for "a composition or protein extract comprising a *T. thermophilis* dUTPase." See Advisory Action, at page 5, item 10. Because this language is similar to the language in claim 87, applicants assume that the Examiner is applying this rejection to claim 87, and those claims that depend from claim 87. Applicants respectfully traverse.

In previous responses, applicants argued that the specification discloses an antibody raised against p45 of *P. furiosus* which recognizes a protein in *Thermus thermophilis*. See e.g., March 2003 Amendment at page 18. Applicants argued that that antibody can be used to identify a *Thermus thermophilis* protein with polymerase-enhancing factor activity. See *id.* However, the examiner argues that because the epitope of the antibody is unknown, the epitope may actually not correlate with dUTPase activity. See May 2003 Action at pages 10 to 11. Furthermore, the Examiner alleges that the specification discloses that there is high structural homology between SEQ ID NO: 71 and dCTPases. See *id.* at page 11.

In the November 2003 Amendment, applicants pointed out that antibody generation when screening for proteins with certain activities is known in the art. See November 2003 Amendment at page 14. Applicants also pointed out that purification is

not necessary to determine whether a putative protein possesses dUTPase activity.

See *id.* Applicants also pointed to *In re Wands*, 858 F. 2d 731, 8U.S.P.Q.2d 1400 (Fed. Cir. 1988), where the specification was found to be enabling for monoclonal antibodies, the structure of which were not necessarily predictable. See *id.* at pages 15 to 16.

Rather than repeat those arguments here, applicants incorporate those arguments from the November 2003 Amendment by reference. In the November 2003 Amendment, applicants also questioned the relevance of the Examiner's allegation concerning the structural homology between SEQ ID NO: 71 and dCTPases. See *id.* at page 15.

In the Advisory Action, the Examiner responds by alleging that there are a potentially large number of antibodies which can bind to the polypeptide of SEQ ID NO: 71. See Advisory Action, page 6, item 12. The Examiner then alleges that "testing an extremely large number of proteins to determine which ones have the desired activity would constitute undue experimentation [absent] some teaching correlating structure with function." See *id.* The Examiner also alleges that "the specification fails to disclose whether the polypeptide of SEQ ID NO: 71 is indeed a dUTPase or a dCTPase...." See Advisory Action at page 7, item 12. The Examiner then alleges that because SEQ ID NO: 71 shares structural homology with dCTPases, the antibody raised against SEQ ID NO: 71 is likely to recognize dCTPases. See *id.* The Examiner also alleges that because that antibody may be specific for a dCTPase, that the protein identified in the *Thermus thermophilis* extract may be a dCTPase. See *id.*

First, the Examiner's argument that there are a potentially large number of antibodies which can bind to the polypeptide of SEQ ID NO: 71, and that, therefore, the antibodies are likely to recognize a large number of proteins which do not have

dUTPase activity is inconsistent with applicants' results described in the specification. Specifically, if the antibody was so non-specific that it recognized large numbers of proteins with no dUTPase activity, then one would expect to see numerous spurious bands on a Western blot rather than a 24 kD band. In fact, applicants were able to identify the 24 kD band in the *Thermus thermophilis* sample. See page 60, lines 6 to 8. Indeed, if one looks at Figure 27, which shows a Western blot of several different cell samples probed with the antibody raised against SEQ ID NO: 71, one can see that the antibody is actually very specific. See page 13, lines 7 to 13, and Figure 27. Thus, the antibody does not recognize "an extremely large number of proteins" as the Examiner alleges.

Second, the Examiner's allegation that the specification fails to disclose whether the polypeptide of SEQ ID NO: 71 is indeed a dUTPase or a dCTPase is incorrect. Example 11 describes both dCTPase and dUTPase assays conducted with cloned p45. See Example 11 at pages 48 to 49. In the analysis, applicants concluded the p45 was a dUTPase. See *id*. Although dCTP can act as a substrate for p45, dUTP was the preferred substrate. See page 49, lines 15 to 18. Thus, the Examiner's argument that p45 is "more likely to be a dCTPase", and, therefore, that any proteins identified by that antibody are more likely to be dCTPases than dUTPases is based on an incorrect assumption. Furthermore, even if the antibody recognized both dCTPase and dUTPase, one skilled in the art would then only have to distinguish between two proteins to identify the dUTPase. As the Examiner admits, "testing a limited number of samples would not constitute undue experimentation...." See Advisory Action, at page 6, item 12.

Third, as applicants have previously noted, applicants can use antibody selection to identify *Thermus thermophilis* protein extracts that comprise purified proteins from *Thermus thermophilis* which may possess dUTPase activity. After this initial selection, applicants can use the test for dUTPase activity described in Example 1, at pages 20 to 22 to test those proteins for dUTPase activity. Indeed applicants have performed those exact series of experiments with a *Thermus thermophilis* extract. See Example 13 at pages 59 to 60. Applicants used the antibody raised against *P. furius* p45 to identify a 24 kD band by Western blot in *Thermus thermophilis* samples. See page 60, at lines 5 to 9. The presence of a dUTPase in the *Thermus thermophilis* samples was then confirmed using a dUTP conversion assay employing reverse phase HPLC. See *id.* at lines 9 to 12. Thus, applicants assert that they have enabled claim 87.

Applicants request reconsideration and withdrawal of the second 35 U.S.C. § 112, first paragraph, enablement rejection in item No. 10.

Rejection (3)

The Examiner rejects certain unspecified claims by alleging that the specification does not reasonably provide enablement for "a composition or protein extract comprising *Thermus thermophilis* proteins and dUTPases from any source." See Advisory Action, at page 5, item 10. Because this language is similar to the language in claim 87, applicants assume that the Examiner is applying this rejection to claim 87, and those claims that depend from claim 87. Solely to expedite prosecution and without acquiescing to the Examiner's rejection, applicants have amended claim 87 to include the language "wherein at least one of the purified proteins from *Thermus*

*thermophilis* possesses dUTPase activity." That amendment should obviate the Examiner's rejection of claim 87.

Applicants request reconsideration and withdrawal of the third 35 U.S.C. § 112, first paragraph, enablement rejection in item No. 10.

**Rejection (4)**

The Examiner rejects certain unspecified claims by alleging that the specification does not reasonably provide enablement for a composition or protein extract comprising a protein of any function which can be detected by an antibody specific for the protein of SEQ ID NO: 71. See Advisory Action, page 5, item 10. Because this language is similar to the language in claim 90, applicants assume that the Examiner is applying this rejection to claim 90, and those claims that depend from claim 90. Solely to expedite prosecution, and without acquiescing to the Examiner's rejection, applicants have amended claim 90 to include the language "wherein the at least one protein of the purified proteins from *Thermus thermophilis* which possesses dUTPase activity can be bound by an antibody specific for a recombinant *P. furiosus* protein consisting of the amino acid sequence of SEQ ID NO: 71." That amendment should obviate the Examiner's rejection of claim 90.

Applicants request reconsideration and withdrawal of the fourth 35 U.S.C. § 112, first paragraph, enablement rejection in item No. 10.

**Rejection (5)**

The Examiner rejects certain unspecified claims by alleging that the specification does not reasonably provide enablement for a composition or protein extract comprising a thermostable DNA polymerase and a composition or protein extract comprising T.

thermophilis dUTPase. See Advisory Action at page 5, line 10. Because both claims 89 and 91 include the language "a thermostable DNA polymerase", applicants assume that the Examiner is applying this rejection to claims 89 and 91. Applicants respectfully traverse.

First, applicants describe compositions comprising a protein extract and a thermostable DNA polymerase in Example 1 of the specification. See specification at pages 20 to 22. Although example 1 describes the use of cell extracts from *Pyrococcus furiosus* in screening assays for PCR-enhancing activity, one skilled in the art could replace the *Pyrococcus furiosus* protein extract with an extract from *Thermus thermophilis* without undue experimentation. One need only make an extract from *Thermus thermophilis*.

With regard to making the extract from *Thermus thermophilis*, as the specification notes, general methods of making extracts from cells were known in the art at the time of filing. See e.g., page 20, lines 3 to 4. And specific methods of making cell extracts are described in the specification. See, e.g. page 20, lines 5 to 10. Finally, the specification describes a dUTPase assay performed on extracts of *Thermus thermophilis*, demonstrating specifically that preparation of *Thermus thermophilis* extracts was within the skill of those skilled in the art. See page 60, lines 5 to 12. Thus, applicants have enabled compositions comprising a *Thermus thermophilis* dUTPase and further comprising a thermostable DNA polymerase.

Applicants request reconsideration and withdrawal of the fifth 35 U.S.C. § 112, first paragraph, enablement rejection in item No. 10.

Rejection (6)

The Examiner rejects certain unspecified claims by alleging that the specification does not reasonably provide enablement for a composition or protein extract comprising a protein of any function which can be detected by an antibody specific for the protein of SEQ ID NO: 71 wherein the protein possesses a molecular weight of approximately 92 kD in an SDS-PAGE gel. See Advisory Action at page 5, line 10. Because that language is similar to the language in claim 92, applicants assume that the Examiner is applying this rejection to claim 92. Applicants have canceled claim 92, thus the Examiner's rejection of claim 92 is moot.

Rejection (7)

The Examiner rejects certain unspecified claims alleging that the specification does not reasonably provide enablement for a composition comprising a *Thermus thermophilis* dUTPase which further comprises a protein of any function having a molecular weight of 24 kD. See Advisory Action at page 5, line 10. Because that language is similar to the language in claim 97, applicants assume that the Examiner is applying this rejection to claim 97. Applicants respectfully traverse.

Applicants have enabled a composition comprising a *Thermus thermophilis* dUTPase as discussed above under Rejection (2). Furthermore, applicants have identified a band of 24 kD in *Thermus thermophilis* samples run out on an SDS-PAGE gel. See p. 60, lines 5 to 8. Therefore, applicants have enabled 97.

Applicants request reconsideration and withdrawal of the seventh 35 U.S.C. § 112, first paragraph, enablement rejection in item No. 10.

**Double Patenting**

The Examiner maintains the rejection of claims 17, 46, 59 to 66, 77 to 79, 85, 87 to 92, 95, and 97 under the judicially created doctrine of double patenting over certain claims of U.S. Patent No. 6,183,997. See Advisory Action at pages 7 to 8, item 14.

As applicants have previously noted, without acquiescing to the rejection, if the claims are otherwise found in condition for allowance, applicants will file a terminal disclaimer.

**Conclusion**

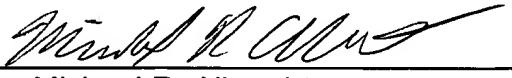
Applicant respectfully asserts that the application is in condition for allowance and requests issuance of a Notice of Allowance. If the Examiner does not consider the application to be in condition for allowance, applicants request that she call the undersigned at (650) 849-6658 to set up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
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Dated: September 13, 2004

By:   
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